

Household transmission of seasonal influenza from HIV-infected and HIV-uninfected individuals in South Africa, 2013-2014

Cheryl Cohen^{1,2}, Akhona Tshangela¹, Ziyaad Valley-Omar^{1,3}, Preetha Iyengar⁴, Claire von Mollendorf^{1,2}, Sibongile Walaza^{1,2}, Orienka Hellferscee^{1,5}, Marietjie Venter^{1,6}, Neil Martinson⁷, Gethwana Mahlase⁸, Meredith McMorrow^{9,10}, Benjamin J. Cowling¹¹, Florette K. Treurnicht¹, Adam L. Cohen^{9,10,12}, Stefano Tempia^{1,9,10}

¹Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases of the National Health Laboratory Service, Johannesburg, South Africa;

²School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa;

³Department of Pathology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

⁴District of Columbia Department of Health, Washington, DC, USA;

⁵School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa;

⁶Centre for Viral Zoonoses, Department of Medical Virology, University of Pretoria

⁷Perinatal HIV Research Unit (PHRU), Klerksdorp-Tshepong Hospital, North West Province, South Africa;

⁸Pietermaritzburg Metropolitan, KwaZulu-Natal, South Africa;

⁹Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America (USA);

¹⁰Influenza Program, Centers for Disease Control and Prevention, Pretoria, South Africa;

¹¹WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region

¹²Expanded Programme on Immunization, Department of Immunizations, Vaccines, and Biologicals, World Health Organization, Geneva, Switzerland

Corresponding author: Cheryl Cohen, Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases, Private Bag X4, Sandringham, 2131, Gauteng, South Africa, Telephone: 27 11 386 6593. Fax: 27 11 882 9979. E-mail: cherylc@nicd.ac.za

Abstract

Background

We estimated the household secondary infection risk (SIR) and serial interval (SI) for influenza transmission from HIV-infected and HIV-uninfected index cases..

Methods

Index cases were the first symptomatic person in a household with influenza-like illness, testing influenza positive on real-time reverse transcription polymerase chain reaction (rRT-PCR). Nasopharyngeal swabs collected from household contacts every four days were tested by rRT-PCR. Factors associated with SIR were evaluated using logistic regression.

Results

We enrolled 28 HIV-infected and 57 HIV-uninfected index cases. On multivariable analysis, HIV-infected index cases were less likely to transmit influenza to household contacts (odds ratio (OR) 0.2 95% CI 0.1-0.6)(SIR 16%, 18/113 vs 27%, 59/220). Factors associated with increased SIR included index age group 1-4 years (OR 3.6, 95% CI 1.2-11.3) and 25-44 years (OR 8.0, 95% CI 1.8-36.7) and contact age group 1-4 years (OR 3.5, 95% CI 1.2-10.3) compared to 5-14 years and sleeping with index case (OR 2.7, 95% CI 1.3-5.5). HIV-infection of index case was not associated with SI.

Conclusions

HIV-infection was not associated with SI. Increased infectiousness of HIV-infected individuals is likely not an important driver of community influenza transmission.

Keywords: influenza, household, transmission, HIV, South Africa

Key points

The seasonal influenza secondary infection risk and serial interval in South Africa is similar to elsewhere. HIV-infected individuals were less likely to transmit influenza. Increased infectiousness of HIV-infected individuals is likely not an important driver of community influenza transmission.

Introduction

HIV is an important risk factor for influenza-associated hospitalisation and death.[1, 2] It is not known whether influenza virus transmission differs between HIV-infected and HIV-uninfected individuals, although this could potentially impact influenza virus community burden in high HIV prevalence settings. A single study from Kenya found that household contacts of HIV-infected index cases with influenza had double the risk of secondary influenza-like illness compared to contacts of HIV-uninfected index cases; however, laboratory testing for influenza was not performed on the household contacts.[3] Early studies of influenza shedding suggested that HIV-infected adults may shed influenza for longer than HIV-uninfected individuals.[4, 5] We hypothesised that HIV-infected individuals might be more likely to transmit influenza to their household contacts.

The household is an important site of influenza transmission in the community and may account for up to 30% of influenza virus transmission events.[6, 7] Factors found to be associated with increased susceptibility to influenza acquisition include younger age of the contact, underlying illness, smoking, relationship to the index case and intensity of exposure measured by close contact with the index case such as shared bedroom or meals.[8] Factors

associated with increased infectivity of the index case in previous studies include young age of the index case, higher or lower number of household contacts and various symptoms.[8]

Influenza virus circulation in South Africa is seasonal during the Southern Hemisphere winter.[9] In South Africa, the national HIV prevalence was 12.2% in 2012, [10] and there were an estimated 7.1 million individuals living with HIV in 2017.[11]

We implemented a study aiming to estimate the household secondary infection risk (SIR) and serial interval (SI) for influenza transmission from HIV-infected and -uninfected index cases separately and to evaluate whether HIV is associated with SIR and SI.

Methods

Study design

We performed a case-ascertained household transmission study during the 2013 and 2014 influenza seasons with enrolment of index cases from May through October each year.[12] Preliminary findings of the overall SIR and SI (not stratified by HIV status) from the 2013 influenza season have been previously described.[13] Assuming an HIV-prevalence of 40% among index cases and an SIR of 10% and 20% in contacts of HIV-uninfected and HIV-infected index cases respectively at a significance level (α) of 0.05 and a power of 0.90 we needed to enrol 80 HIV-infected and 120 HIV-uninfected index cases.

Study population and enrolment

The study was conducted in two peri-urban, temperate communities; Klerksdorp in the Northwest Province and Pietermaritzburg in KwaZulu-Natal Province, South Africa.

Outpatients presenting to primary health care facilities (4 in Klerksdorp and 2 in Pietermaritzburg in 2013 and 2 at each site in 2014) were screened for influenza-like illness

(ILI) (defined as acute respiratory infection with measured temperature of $\geq 38^{\circ}\text{C}$ or self-reported fever and cough). Eligible index cases were the first symptomatic individual in a household with three-or-more members, presenting with ILI of ≤ 3 days symptom duration with a positive influenza rapid diagnostic test (IRDT) from a nasopharyngeal/oropharyngeal (NP/OP) swab at the time of screening subsequently confirmed by real-time reverse transcription polymerase chain reaction (rRT-PCR) assay and consenting to HIV testing. Point of care testing was conducted using the Becton Dickinson (BD) Veritor™ system Flu A+B IRDTs in 2013 and the BD Directigen™ Flu A+B in 2014. Index cases with initially positive IRDT but subsequently negative rRT-PCR and their household contacts were withdrawn.

Household contacts included any individual who regularly ate or slept in the same household as the index case for four or more days a week during the exposure period (one day before to twelve days after onset of illness in the index case). At least 70% of household members had to agree to participate for the household to be included. Household contacts were enrolled within 48 hours of index case recruitment. At the time of enrolment for index cases and contacts we collected information on demographics, medical conditions, recent and current symptoms and type of contact between household contacts and the index case.

Follow up

Household contacts were followed up on day 0, 4, 8 and 12 post-enrolment, with collection of NP/OP swabs at home or in the clinic from all contacts regardless of illness. We extended follow up to 12 days because we hypothesised that HIV-infected individuals might have prolonged shedding of influenza virus.

At each follow-up visit, a brief questionnaire assessing presence of symptoms was administered. Children aged ≤ 5 years had proxy reporting of symptoms by the primary

caregiver or head of household. If a household contact was unavailable, the study teams attempted two re-visits.

Laboratory testing

NP/OP swab samples from index cases were collected in 10ml Copan Universal Transport Medium™ system (UTM; Copan Universal, Murrieta, California, USA) and stored at 4°C in a refrigerator. During follow-up visits NP/OP swabs were collected from household contacts and stored in PrimeStore® Molecular Transport Medium (MTM; Longhorn Vaccines and Diagnostics, Bethesda, Maryland, USA) in order to obtain high quality nucleic acids.

Samples were transported to the National Institute for Communicable Diseases (NICD) in Johannesburg within the next 48 hours for testing.

All respiratory specimens had total nucleic acid extraction performed on the MagNA Pure 96 or MagNA Pure LC instruments (Roche, Mannheim, Germany) and were tested by multiplex rRT-PCR for influenza virus A and B as well as parainfluenza virus types 1-3, respiratory syncytial virus, enterovirus, human metapneumovirus, adenovirus and human rhinovirus.[14]

Samples testing positive for influenza A viruses were subtyped for seasonal influenza A(H1N1)pdm09, and A(H3N2) by rRT-PCR using the CDC Influenza Virus Real-time RT-PCR.[15] The viral load of influenza was inferred from the PCR cycle threshold (Ct) values, and is inversely proportional to the PCR Ct value, i.e. the higher the Ct value the lower the viral load.

HIV status of index cases was ascertained by human immunodeficiency virus (HIV) testing according to national protocols at the time of enrolment using rapid HIV testing (Homemed HIV1/2 first screening test and ABON™ HIV1/2 Tri-Line test confirmatory test), review of laboratory-confirmed results in patient notes or verbal reporting of a positive HIV test. A

documented negative test result from the last 6 weeks was also considered valid. Household contacts were also offered HIV testing, but consent to testing was not required for study participation.

Statistical analysis

We defined laboratory-confirmed secondary or tertiary household contacts as those with a positive result for influenza virus by rRT-PCR testing of one or more NP/OP specimens collected during follow-up that corresponded to the influenza type of the index case, regardless of symptoms. Proportions were compared using the Chi squared or Fisher's exact test depending on numbers. The household SIR was estimated as the proportion of household contacts that had laboratory-confirmed influenza virus infection. This is an overall measure of transmission in the household acknowledging that some cases may have been tertiary cases and some infections may have been acquired outside the household.[8] To minimise potential bias, for the analysis of factors associated with SIR we restricted to individuals testing influenza positive within the first 8 days of follow up because individuals testing influenza positive after 8 days have an increased likelihood of being tertiary cases.[8] We compared the characteristics of index cases and household contacts, HIV-infected and -uninfected index cases and factors associated with SIR using logistic regression. We controlled for characteristics of the index case and household contact in the same multivariable model. We performed a sensitivity analysis of factors associated with SIR including all enrolled contacts. Eligible contacts that refused enrolment (n=25, 7%) were excluded from the main analysis. We performed a sensitivity analysis of the SIR in which non-enrolled eligible contacts were considered uninfected to explore the effect of this assumption.

Symptomatic household contacts were defined as individuals reporting at least one symptom including: fever, sore throat, cough/difficulty breathing, muscle aches, nasal congestion,

diarrhoea, or headache. SI was calculated as the difference between the date of first symptom onset in the index case and in the secondary case. For the analysis of SI we restricted to household contacts with symptom onset within 8 days of symptom onset in the index case. This was because we hypothesised that individuals with later symptom onset were more likely to be tertiary cases and because in our setting the mean influenza shedding duration is 7 days.[16] We evaluated factors associated with SI using Weibull accelerated failure time regression.

We accounted for within-household clustering using the Taylor-linearized variance estimation (“svy” Stata function) after setting households as primary sampling units. For the multivariable models we assessed all variables that were significant at $p < 0.2$ on univariate analysis, and dropped non-significant factors ($p \geq 0.05$) with manual backward elimination. HIV was retained a-priori as this was the main exposure of interest. Pairwise interactions were assessed by inclusion of product terms for all variables remaining in the final multivariable additive model. We conducted all statistical analyses using STATA version 14.1 (Stata Corp LP, College Station, Texas). For each univariate analysis, we used all available case information. In the multivariable models, patients with missing data for included variables were dropped from the model.

Ethics

Ethical approval was obtained from the University of the Witwatersrand and KwaZulu-Natal and the Centers for Disease Control and Prevention with reliance on the local ethical approvals. Written informed consent or assent was obtained from all participants or their caregivers. Participants who attended follow-up visits at the clinic were compensated for transport. There was no other compensation.

Results

We enrolled 94 index cases based on positive IRDT results; seven of these subsequently tested influenza negative on rRT-PCR and were excluded, resulting in 87 enrolled index cases (57 influenza A(H3N2), 17 influenza A(H1N1)pdm09, 3 influenza A(untyped), 10 influenza B) with 333 enrolled household contacts (Figure 1). Of the index cases, 28 (32%) were HIV-infected, 64% (18/28) of whom reported taking ART and 53% (8/15) of those with available data had a CD4+ T cell count ≥ 500 cells/mm³ (Table 1). Among index cases, 23% (20/87) were aged <5 years compared to 10% (34/333) of household contacts (p=0.002). Among household contacts, HIV status was available for 50% (166) of individuals, of whom 16% (26/166) were HIV-infected. A low percent of index cases (1/79, 1%) and household contacts with available data (12/271, 4%) reported receiving the influenza vaccine. All study participants were of black race. The median household size was 6 individuals including the index case (interquartile range (IQR) 3-11) and the median number of rooms per house was 4 (IQR 2-5). On univariate analysis, compared to HIV-uninfected index cases, HIV-infected index cases were significantly more likely to be aged 25-44 years (odds ratio (OR) 44.2, 95% confidence interval (CI) 4.6-425.7) or 45-64 years (OR 26.0 95% CI 2.2-304.7) compared to 15-24 years (Supplementary table 1). Symptoms were similar in HIV-infected and -uninfected index cases.

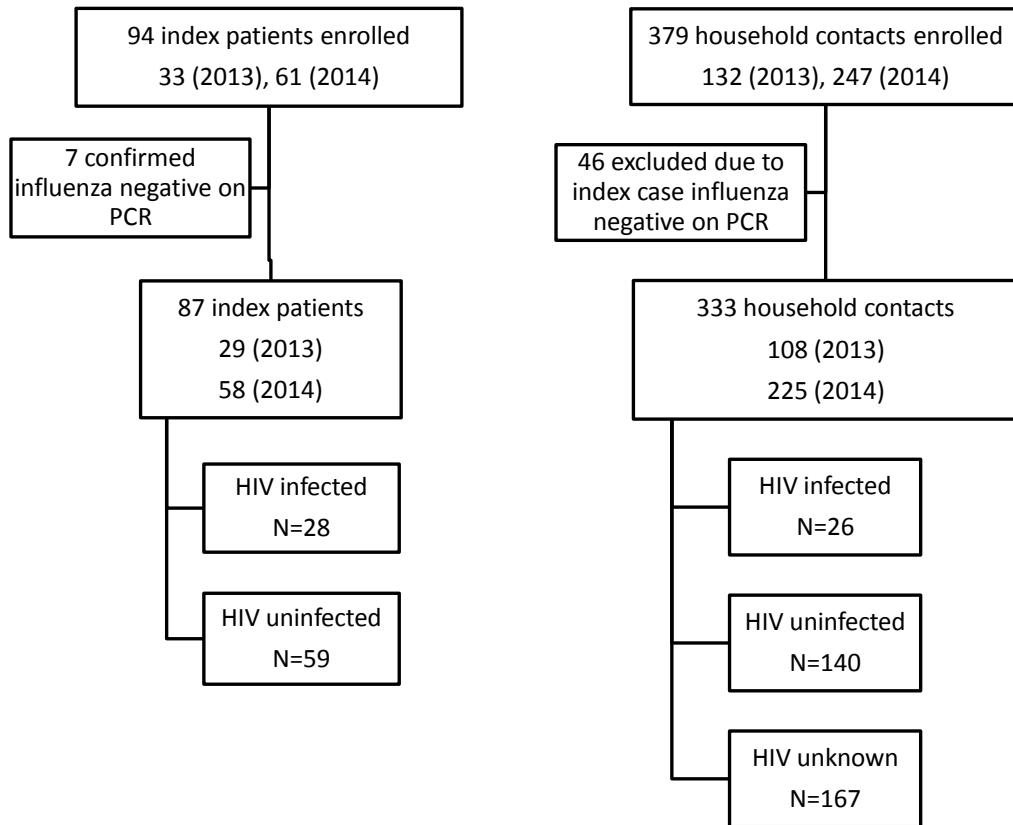


Figure 1: Flow chart of index cases and household contacts enrolled in Klerksdorp and Pietermaritzburg, South Africa, 2013-2014

Table 1: Characteristics of influenza-positive index cases and their household contacts, Klerksdorp and Pietermaritzburg in South Africa, 2013-2014

Characteristic	Index case n/N (%) N=87	Household contact n/N (%) N=333
Age group (years)		
<1	2/87 (2)	6/333 (2)
1-4	18/87 (21)	28/333 (8)
5-14	22/87 (25)	82/333 (25)
15-24	14/87 (16)	76/333 (23)
25-44	22/87 (25)	84/333 (25)
45-54	9/87 (10)	40/333 (12)
≥65	0/87 (0)	17/333 (5)
Female	52/87 (60)	200/309 (65)
Pietermaritzburg site		
2014 (vs 2013)	58/87 (67)	225/333 (68)
Alcohol use ^a	13/41 (32)	57/202 (28)
Smoking ^a	8/41 (20)	33/202 (16)
Underlying medical condition (not HIV) ^b	2/87 (2)	12/333 (4)
HIV-infected	28/87 (32)	26/140 (19) ^e
Currently taking antiretroviral therapy ^c	18/28 (64)	No data
CD4+ T cell count (/mm³)^c		
<200	2/15 (13)	No data
200-500	5/15 (33)	
≥500	8/15 (53)	
Currently taking treatment for tuberculosis	3/79 (4)	6/249 (2)
Received influenza vaccine	1/79 (1)	12/271 (4)
Household contacts only		
Relationship with index case		
Parent		56/287 (20)
Spouse		7/287 (2)
Child		54/287 (19)
Sibling		58/287 (20)
Other relative		112/287 (39)
Contact with index case		
Share a bed		86/312 (28)
Share a cup or plate		73/312 (23)

Household level characteristics

>3 people per room	26/87 (30)
Number in household (excluding index case)	
2-3	30/87 (34)
4-6	49/87 (56)
7+	8/87 (9)
≥2 secondary cases in household	18/87 (21)
Smoking exposure in home ^d	7/57 (12)
Home has a tap indoors ^d	18/58 (31)
Soap available for hand washing ^d	30/57 (53)
Cook with electric stove ^d	54/58 (93)

Data missing for sex (n=24), HIV status (n=193), use of antiretroviral therapy (n=36), CD4+ T cell count (n=39), current tuberculosis treatment (n=92), receipt of influenza vaccine (n=100), contact relationship with index case (n=46), contact with index case (n=21), smoking exposure in the home (n=30), home has a tap indoors (n=29), soap available for hand washing (n=30), cook with an electric stove (n=29).

^aSelf reported, among individuals aged >15 years

^bAsthma, other chronic lung disease, chronic heart disease, liver disease, renal disease, diabetes mellitus, immunocompromising conditions excluding HIV infection, neurological disease or pregnancy. Comorbidities were considered absent in cases for which the medical records stated that the patient had no underlying medical condition or when there was no direct reference to that condition.

^camong HIV-infected, of individuals taking antiretroviral therapy with available data 0 had a CD4+ T cell count <200/mm³, 4 were 200-500/mm³ and 6 were ≥500/mm³

^dInformation only available for households who completed a detailed household information questionnaire

^eHIV-status information missing for 167 (50%) household contacts

Table 2: Characteristics of index case and household contacts associated with household secondary infection risk (SIR) analysis including individuals testing influenza positive in the first 8 days, Klerksdorp and Pietermaritzburg in South Africa, 2013-2014

Characteristic	SIR ^a n/N (%)	Univariate OR (95% CI)	p	Multivariable OR (95% CI)	p
Index case characteristics					
Age group (years)					
<1	0/6 (0)	Not estimated		Not estimated	
1-4	24/62 (39)	2.5 (1.2-5.6)	0.019	3.6 (1.2-11.3)	0.026
5-14	17/86 (20)	Reference	Reference	Reference	Reference
15-24	11/56 (20)	1.0 (0.4-2.7)	0.987	1.9 (0.6-6.4)	0.280
25-44	21/85 (25)	1.3 (0.6-3.2)	0.520	8.0 (1.8-36.7)	0.007
45-64	4/38 (11)	0.5 (0.1-3.0)	0.426	2.6(0.3-22.6)	0.395
≥65	0/0 (0)	Not included		Not included	
Sex					
Male	30/122 (25)	1.1 (0.6-1.9)	0.706		
Female	47/211 (22)	Reference	Reference		
Site					
Klerksdorp	49/177 (28)	1.8 (0.9-3.5)	0.111		
Edendale	28/156 (18)	Reference	Reference		
Year					
2013	19/108 (18)	Reference	0.149		
2014	58/225 (26)	1.6 (0.9-3.2)			
HIV status					
Uninfected	59/220 (27)	Reference	Reference	Reference	Reference
Infected	18/113 (16)	0.5 (0.2-1.3)	0.158	0.2 (0.1-0.6)	0.007
HIV status					
Uninfected	59/215 (27)	Reference	Reference		
Infected, receiving ART	13/77 (17)	0.5 (0.2-1.7)	0.304		
Infected, not receiving	5/36 (14)				
ART					
		0.4 (0.2-0.9)	0.034		
Non HIV underlying illness ^d					
Absent	77/326 (24)	Not estimated			
Present	0/7 (0)				
Currently taking treatment for tuberculosis					

No	61/281 (22)	Reference	0.002		
Yes	9/15 (60)	5.4 (2.4-12.2)			
Alcohol use					
No	24/89 (27)	2.8 (0.6-8.0)	0.171		
Yes	5/43 (12)	Reference			
Smoking					
No	25/108 (34)	1.5 (0.5-7.0)	0.591		
Yes	4/24 (17)	Reference			
Influenza type					
A	71/294 (24)	Reference	0.579		
B	12/39 (31)	1.4 (0.4-4.7)			
Influenza type and subtype					
H3N2	52/219 (24)	1.4 (0.7-2.9)	0.405		
H1N1pdm09	12/65 (18)	Reference	Reference		
A (Unsubtyped)	2/10 (20)	1.1 (0.2-7.9)	0.921		
B	11/39 (28)	1.7 (0.7-6.4)	0.404		
Influenza cycle threshold (Ct) value					
<30	64/243 (26)	2.3 (1.1-4.8)	0.036	2.7 (1.2-6.1)	0.020
≥30	12/88 (14)	Reference	Reference	Reference	Reference
Pneumococcal colonisation					
Yes	37/131 (28)	0.9 (0.4-2.4)	0.909		
No	22/75 (29)	Reference			
Viral coinfection ^b					
Yes	15/64 (23)	1.0 (0.5-2.2)	0.947		
No	62/269 (23)	Reference			
Received influenza vaccine					
Yes	0/5 (0)	Not estimated			
No	69/298 (23)				
Sore throat					
Yes	21/135 (16)	0.4 (0.2-0.9)	0.032		
No	50/173 (29)	Reference	Reference		
Myalgia					
Yes	9/64 (14)	0.5 (0.2-1.4)	0.176		
No	62/244 (25)	Reference			
Household contact characteristics					

Age group (years)					
<1	3/6 (50)	3.3 (0.6-13.6)	0.095	1.6 (0.3-5.8)	0.466
1-4	13/28 (46)	2.8 (1.1-7.6)	0.035	3.5 (1.2-10.3)	0.021
5-14	19/82 (23)	Reference	Reference	Reference	Reference
15-24	11/76 (14)	0.6 (0.2-1.3)	0.169	0.5 (0.2-1.2)	0.115
25-44	16/84 (19)	0.8 (0.4-1.7)	0.528	0.8 (0.3-1.7)	0.535
45-64	9/40 (23)	1.0 (0.3-2.7)	0.941	0.9 (0.3-3.0)	0.832
≥65	6/17 (35)	1.8 (0.6-5.5)	0.294	2.4 (0.6-9.3)	0.216
Sex					
Male	26/109 (24)	1.0 (0.6-1.8)	0.865		
Female	46/200 (23)	Reference			
HIV status					
Uninfected	38/140 (27)	Reference	0.454		
Infected	5/26 (19)	0.6 (0.2-2.1)			
Non HIV underlying illness ^d					
Absent	75/321 (23)	Reference	0.573		
Present	2/12 (17)	0.5 (0.1-2.9)			
Alcohol use ^c					
No	30/145 (21)	Reference	Reference		
Yes	10/57 (18)	0.8 (0.3-1.8)	0.647		
Smoking ^c					
No	33/169 (21)	Reference	Reference		
Yes	7/33 (21)	1.1 (0.4-2.8)	0.825		
Received influenza vaccine					
Yes	2/12 (17)	Reference	0.734		
No	54/259 (21)	1.3 (0.3-6.6)			
Share a bed with the index case					
Yes	29/86 (34)	2.0 (1.1-3.8)	0.021	2.7 (1.3-5.5)	0.009
No	45/226 (20)	Reference		Reference	Reference
Number of people in household					
2-3	12/85 (14)	Reference	Reference	Reference	Reference
4-6	43/195 (23)	1.7 (0.7-4.0)	0.213	2.3 (0.7-7.6)	0.180
7+	22/53 (42)	4.3 (1.4-13.3)	0.012	6.1 (1.3-28.4)	0.022
People per room					
<3	52/225 (23)	Reference	0.358		
≥3	30/108 (28)	1.3 (0.8-2.2)			

Number of children aged			
<5 years in house			
≤2			
>2	64/315 (20)	Reference	<0.001
	13/18 (72)	10.2 (7.1-14.7)	

OR – Odds ratio, CI – confidence interval

Missing data: Out of 87 index cases included in the analysis, data were missing for alcohol use (n=4), smoking (n=4), current tuberculosis treatment (n=8), received influenza vaccine (n=8), influenza cycle threshold value (n=1), pneumococcal colonization (n=34), symptoms (sore throat, runny nose, headache and myalgia) (n=7). Out of 333 household contacts included in the analysis data were missing for contact sex (n=24), contact HIV status (n=167), contact alcohol use (n=15), contact smoking (n=15), contact influenza vaccine receipt (n=62), contact sharing a bed with index (n=21). There were 70 (21%) household contacts missing one follow-up sample, 20 (6%) missing two samples and 31 (9%) missing three samples.

Odds ratios and p values for all variables included in the multivariable models are displayed in the two right hand columns of the table. No pairwise interactions were included in the multivariable models as no interaction terms were found significant. Additional factors evaluated but not found to be associated with SIR were sharing eating utensils with the index case, avoiding contact with the sick household member.

^aSecondary infection risk (SIR)=Number of secondary cases in the household/number of exposed household contacts

^bTest positive on polymerase chain reaction for at least one of parainfluenza virus types 1-3, respiratory syncytial virus, enterovirus, human metapneumovirus, adenovirus or human rhinovirus

^cAmong individuals aged >15 years

^dAsthma, other chronic lung disease, chronic heart disease, liver disease, renal disease, diabetes mellitus, immunocompromising conditions excluding HIV infection, neurological disease or pregnancy. Comorbidities were considered absent in cases for which the medical records stated that the patient had no underlying medical condition or when there was no direct reference to that condition.

Overall, 88 household contacts tested influenza positive, of whom 83 had the same influenza type or subtype as the index case (SIR 25% [83/333], 95% CI 20%-30%). These were 54 influenza A(H3N2), 9 influenza A(H1N1)pdm09, 8 influenza A(untyped), 12 influenza B. Restricting our analysis to household contacts who tested influenza positive in the first 8 days the SIR was 23% (77/333, 95%CI 19%-28%). Sensitivity analysis assuming 25 household members not enrolled were influenza negative gave a secondary infection risk of 22% (77/358, 95% CI 17%-26%). On multivariable analysis, HIV-infected index cases were significantly less likely to transmit influenza (SIR 16%, 18/113) compared to HIV-uninfected index cases (SIR 27%, 59/220 adjusted odds ratio (aOR) 0.2 95% CI 0.1-0.6) (Table 2). Factors associated with increased SIR were index case age group 1-4 years (aOR 3.6, 95% CI 1.2-11.3) and 25-44 years (aOR 8.0, 95% CI 1.8-36.7) compared to 5-14 years, household contact age group 1-4 years (aOR 3.5, 95% CI 1.2-10.3) compared to 5-14 years, sharing a bed with the index case (aOR 2.7, 95% CI 1.3-5.5), high viral load in index case (cycle threshold value <30) (aOR 2.7, 95% CI 1.2-6.1) and >7 people in the household (aOR 6.1, 95% CI 1.3-28.4) compared to 3-4 people. On sensitivity analysis including all household contacts who tested influenza positive with the same subtype as the index case, factors associated with transmission remained unchanged (Supplementary table 2).

Among 213 (64%) household contacts with available symptom data, influenza-positive individuals were more likely than influenza-negative individuals to report any symptom (79%, 46/58 vs 62%, 96/155 p=0.017), ≥ 2 symptoms (71%, 41/58 vs 50%, 78/155 p=0.009) and fever and cough (48%, 28/58 vs 18%, 28/155 p<0.001). Among 46 symptomatic influenza-positive contacts with available date of symptom onset, 72% (33) had symptoms prior to the first influenza positive test, 17% (8) reported symptom onset on the same day and 11% (5) reported symptom onset after the first influenza positive test. Among influenza-positive contacts, cough and nasal congestion were more commonly reported among children

aged <5 years and muscle pain and headache among individuals aged ≥ 5 years

(Supplementary table 3). Forty two individuals reported a symptom within 8 days of onset of the index case and were included in the analysis of SI (Figure 2).

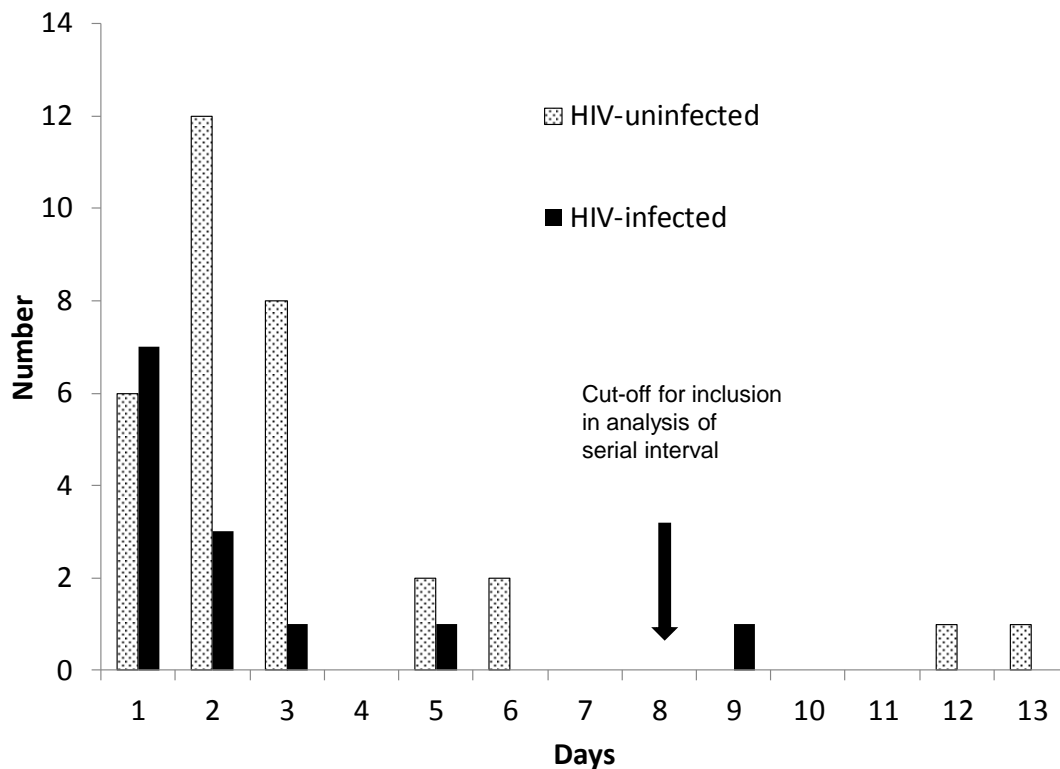


Figure 2: Interval between onset of symptoms in the index case and onset of symptoms in household contacts with laboratory confirmed influenza (serial interval) by HIV-infection status of the index case, Klerksdorp and Pietermaritzburg South Africa, 2013-2014 (n=45)

The median SI in all participants was 2.3 days (range 1-6 days). On multivariable analysis, HIV infection was not associated with SI. SI was significantly shorter for index cases aged 25-44 years (aHR 3.1, 95% CI 1.1-8.6) compared to 5-14 years and for household contacts aged <1 year (aHR 7.8, 95% CI 3.6-15.2) compared to 5-14 years (Table 3).

Table 3: Factors associated with serial interval in 42 secondary cases with symptom onset within 8 days of the index case, Klerksdorp and Pietermaritzburg in South Africa, 2013-2014^a

Characteristic	Serial interval in days Mean ± standard deviation (range)	Univariate hazard ratio (95% CI)	p	Multivariable hazard ratio (95% CI)	p
Index case characteristics					
Age group (years)					
<1					
1-4	Not estimated			Not estimated	
5-14	2.3±0.8 (1-3)	2.2 (0.8-6.0)	0.107	1.6 (0.5-5.6)	0.422
15-24	2.9±2.1 (1-6)	Reference	Reference	Reference	Reference
25-44	2.8±1.7 (1-6)	1.2 (0.3-4.0)	0.804	1.2 (0.3-4.2)	0.760
45-64	1.9±1.1 (1-5)	2.7 (1.1-6.4)	0.033	3.1 (1.1-8.6)	0.029
≥65	2.0±0 (2-2)	3.2 (1.1-9.1)	0.035	0.6 (0.1-5.0)	0.600
	Not estimated			Not estimated	
Sex					
Male	2.4±1.2 (1-6)	Reference	Reference		
Female	2.2±1.5 (1-6)	1.1 (0.5-2.2)	0.822		
Site					
Klerksdorp	2.1±1.4 (1-6)	Reference	Reference		
Edendale	2.8±1.3 (2-6)	0.6 (0.3-1.2)	0.170		
Year					
2013	1.7±0.7 (1-3)	Reference	Reference		
2014	2.6±1.5 (1-6)	0.4 (0.2-0.8)	0.016		
HIV status					
Uninfected	2.5±1.4 (1-6)	Reference	Reference	Reference	0.159
Infected	1.8±1.2 (1-5)	1.8 (1.2-2.9)	0.010	2.0 (0.7-5.7)	
Influenza type and subtype					
H3N2	2.8±1.4 (1-6)	Reference	Reference		
H1N1pdm09	1.8±0.9 (1-3)	2.6 (1.3-5.4)	0.013		
B	1.6±1.3 (1-5)	2.5 (1.5-4.1)	0.001		
A (Unsubtyped)	2.0±0 (2-2)	2.4 (1.5-4.0)	0.001		
Influenza cycle threshold (Ct) value*					
<30	2.4±1.4 (1-6)	0.6 (0.3-1.1)	0.106		
≥30	2.0±0.8 (1-3)	Reference	Reference		

Sore throat*					
Yes	3.5±1.6 (2-6)	0.3 (0.1-0.5)	0.001		
No	1.9±1.0 (1-5)	Reference	Reference		
Runny nose*					
Yes	2.5±1.5 (1-6)	0.4 (0.2-0.9)	0.032		
No	1.7±0.9 (1-3)	Reference	Reference		
Cough*					
Yes	2.3±1.3 (1-6)	0.4 (0.1-0.9)	0.046		
No	1.5±0.7 (1-2)	Reference	Reference		
Household contact characteristics					
Age group (years)					
<1					
1-4	1.0±0 (1-1)	9.8 (3.5-27.4)	<0.001	7.8 (3.9-15.2)	<0.001
5-14	2.3±1.6 (1-6)	1.3 (0.4-4.5)	0.681	2.5 (0.4-14.8)	0.303
15-24	2.6±1.8 (1-6)	Reference	Reference	Reference	Reference
25-44	2.4±1.4 (1-5)	1.3 (0.4-4.0)	0.631	3.0 (0.7-12.3)	0.130
45-64	2.4±1.2 (1-5)	1.4 (0.5-4.0)	0.506	3.6 (0.7-18.5)	0.115
≥65	1.7±0.8 (1-3)	3.0 (0.9-9.3)	0.062	8.8 (0.9-83.5)	0.058
	3.0±0 (3-3)	1.1 (0.5-2.5)	0.819	1.3 (0.3-5.1)	0.691
Sex*					
Male	2.5±1.6 (1-6)	Reference	Reference		
Female	2.3±1.3 (1-6)	1.2 (0.5-2.8)	0.677		
HIV status*					
Uninfected	2.3±1.3 (1-6)	Not estimated			
Infected	Not estimated				

Odds ratios and p values for all variables included in the multivariable models are displayed in the two right hand columns of the table. No pairwise interactions were included in the multivariable models as no interaction terms were found significant.

*Data missing for influenza cycle threshold (Ct) value (n=2), sore throat (n=25), runny nose (n=25), cough (n=25), contact sex (n=24), contact HIV status (n=167)

^aAdditional factors evaluated but not found to be associated with serial interval. Index case characteristics: Non HIV-related underlying illness, receiving tuberculosis treatment, alcohol use, smoking, pneumococcal colonization, viral coinfection, influenza vaccine receipt, signs and symptoms (fever, myalgia, headache). Household contact characteristics: share bed with index case, alcohol use, smoking, non HIV underlying illness, influenza vaccine receipt, number of people in the household, number of people per room, number of children aged <5 years in the house.

Discussion

In contrast to our hypothesis of increased influenza transmission from HIV-infected individuals, we found that HIV-infected individuals were significantly less likely to transmit influenza to their household contacts after adjusting for age and household size. Other factors significantly associated with influenza transmission were age of the index case and household contact, large household size and sharing a bed with the index case. The household SIR for laboratory-confirmed influenza was high, with one in four household contacts becoming infected. Approximately one in five PCR-confirmed secondary influenza virus infections were asymptomatic.

Our estimate of SIR of 25% is within the range reported by other studies (1%-38% in a recent review) and similar to preliminary estimates of 19% from the first year of the same study.[8, 13, 17] HIV-infected individuals were significantly less likely to transmit influenza, even adjusting for age and other potential confounding factors. Tuberculosis is an example of a respiratory disease where HIV-infected individuals are less likely to transmit infection compared to HIV-uninfected individuals.[18, 19] In the case of tuberculosis, this is because the disease is less likely to form cavities in the lungs and be released in sputum. It is unclear if there may be analogous mechanisms for influenza. It is also possible that HIV-infected individuals are more likely to avoid contact with other household members or to engage in behaviour such as hand washing, which may reduce transmission when ill with influenza, although we were not able to evaluate this, as we did not collect information on index case behaviour. Some studies have found an association between SIR and symptoms, although findings were not consistent.[8, 20-22] We did not find symptoms to be associated with SIR in our model, nor did we find differences in symptoms between HIV-infected and -uninfected index cases. We were not able to evaluate symptoms in contacts by HIV status due to limited available data.

We had hypothesised that HIV-infected individuals would be more likely to transmit influenza based on reports of increased shedding duration in this group.[4, 5] We conducted a shedding study at the same sites as our transmission study and found that influenza virus shedding duration and initial influenza viral load were similar in HIV-infected and -uninfected individuals.[16] However, in this study, HIV-infected individuals with CD4 counts ≤ 200 cells/mm³ shed influenza virus for longer than those with higher CD4 counts. In our study population, 64% of index cases reported taking ART and 50% with available data had a CD4 count ≥ 500 cells/mm³, suggesting that the majority of subjects were not severely immunosuppressed. We were not powered to assess influenza transmission stratified by level of immunosuppression, but we cannot exclude the possibility of increased transmission from severely immunosuppressed individuals. A previous study found a similar influenza virus shedding duration in HIV-infected individuals receiving ART to HIV-uninfected individuals.[23]

We found that index cases aged 1-4 years were more likely to transmit influenza and household contacts aged 1-4 years were more likely to acquire infection, suggesting an important role for this age group in community influenza transmission. Several studies have found children to be more likely to transmit influenza than adults.[8, 12, 24-26] Interestingly, we also found on adjusted analysis that adults aged 25-44 years were significantly more likely to transmit influenza. This suggests that, in an African setting, young adults may play a more important role in influenza transmission, than previously described. Additional factors found to be associated with influenza transmission included large household size and sharing a bed with the index case. Both large and small household size as well as close contact, such as sharing a bed, have been shown to be associated with increased transmission.[8, 25, 27-29] We also found that a low cycle threshold value of the index case, a proxy for increased nasopharyngeal viral load, was associated with increased transmission, similar to previous

studies.[8, 24] We found no statistically significant difference in serial interval between HIV-infected and -uninfected index cases. Household contacts aged <1 years had a shorter serial interval, previous studies have generally found shorter serial interval in younger individuals.[30]

A strength of our approach is that all household contacts were sampled for PCR testing irrespective of symptoms. This is important as 21% of PCR-confirmed secondary cases did not report any symptoms, which is within the range found in other similar studies of 4%-28%.[31] Numbers of asymptotically infected individuals (n=12) were too small to allow us to evaluate predictors of asymptomatic infection in contacts. Other strengths of our study included complete HIV status information for index cases and the relatively large number of HIV infected index cases, although we did not achieve our projected sample size.

Our study had a number of limitations. We were missing HIV status information on 50% of household contacts, therefore we were not able to assess the effect of HIV status of the household contact on acquisition of influenza virus infection. We also had missing data on CD4 counts of index cases, limiting our ability to evaluate the impact of immunosuppression on disease transmission. However, we did have information on receipt of ART for all index cases and the majority of individuals were receiving ART. It is possible that some of the infections in household contacts were acquired from outside the household leading to overestimation of the SIR. However, results of both modelling and sequencing studies from different settings indicate that the vast majority of infections in household contacts in the first week after onset in the index case will have been acquired within the household.[8, 24, 32, 33] We did identify 5 of 88 secondary infections with differing type/subtype which is consistent with a small proportion of secondary cases acquiring infection outside the household (even with matching type/subtype). Furthermore, in some households in our study the index case may not have been the primary (i.e., initial) case in the household, for example

if the primary case had very mild infection that was missed, or an asymptomatic infection. Because of the short incubation period of influenza, some cases in household contacts could have been tertiary cases.[8] In addition, our approach assumes that the study population is a single homogenous population, which is an oversimplification because each household is its own population and differences between household characteristics may affect SIR.[34, 35] More complex statistical analyses have been described which take this into account and could be explored in future analyses. [17, 36] We did ask about symptoms in all household members at baseline and did not identify any recent illnesses in contacts. We performed an analysis pooling data for all influenza strains over two seasons. It may not be correct to assume that SIR and SI are identical for all strains and seasons, although we did not identify significant differences by these characteristics. We did not achieve our target sample size of 80 HIV-infected and 120 HIV-uninfected index cases because enrolled case numbers were lower than expected.

In conclusion, we found that HIV-infected index cases are less likely than HIV-uninfected individuals to transmit influenza virus infection to their household contacts. This suggests that even in high HIV prevalence settings, increased infectiousness of HIV-infected individuals not an important driver of community influenza transmission. In our setting, children aged 1-4 years and adults aged 25-44 years are more likely to transmit influenza. These age groups could potentially be targeted by vaccination strategies aiming to reduce community transmission. Further studies from different settings may be helpful to verify our findings and understand the mechanism behind the reduced influenza transmission from HIV infected individuals. This should include evaluation of the impact of degree of immunosuppression and ARVs on transmission as well as evaluation of symptoms and behaviour patterns of HIV-infected individuals with influenza.

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Author's contributions

Conception and design of study: CC, PI, CvM, SW, OH, MV, BC, ALC, ST

Data collection and laboratory processing: CC, AT, PI, CvM, ZVO, SW, OH, MV, NM, GM, BC, ALC, ST

Analysis and interpretation: CC, AT, PI, CvM, ZVO, SW, OH, MV, NM, GM, MM, BC, ALC, ST

Drafting or critical review of the article: CC, AT, PI, CvM, ZVO, SW, OH, MV, NM, GM, MM, BC, ALC, ST

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Disclaimer. The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the CDC.

Ethics

Ethical approval was obtained from the University of the Witwatersrand and KwaZulu-Natal and the Centers for Disease Control and Prevention with reliance on the local ethical approvals. Written informed consent or assent was obtained from all participants or their caregivers. Participants who attended follow-up visits at the clinic were compensated for transport. There was no other compensation.

Conflicts of interest

CC has received grant support from Sanofi Pasteur, Advanced Vaccine Initiative, US Centers for Disease Control and Prevention and payment of travel costs from Parexel. The other authors declare no conflict of interest.

Meetings where information has been previously presented

Transmission of respiratory viruses: from basic science to evidence based options for control, 19-21 June 2017, Hong Kong. Household transmission of seasonal influenza from HIV-infected and -uninfected individuals in South Africa, 2013-2014. Cheryl Cohen, Akhona Tshangela, Preetha Iyengar, Claire von Mollendorf, Ziyaad Valley-Omar, Sibongile Walaza, Orienka Hellferscee, Marietjie Venter, Neil Martinson, Gethwana Mahlase, Meredith McMorrow, Ben Cowling, Adam L. Cohen, Stefano Tempia

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Supplementary Material

Supplementary Table 1: Comparison of characteristics of HIV-infected and -uninfected influenza-positive index cases, Klerksdorp and Pietermaritzburg in South Africa, 2013-2014

Characteristic	HIV infected n/N (%) N=28	HIV uninfected (%) N=59	Univariate OR (95% CI)	p
Age group (years)				
<1	1/28 (4)	1/59 (2)	13.0 (0.4-405)	0.144
1-4	1/28 (4)	17/59 (29)	0.8 (0.1-13.4)	0.854
5-14	2/28 (7)	20/59 (34)	1.3 (0.1-15.8)	0.837
15-24	1/28 (4)	13/59 (22)	Reference	Reference
25-44	17/28 (61)	5/59 (8)	44.2 (4.6-425.7)	0.001
45-64	6/28 (21)	3/59 (5)	26.0 (2.2-304.7)	0.009
≥65	0/28 (0)	0/59 (0)	Not included	
Female	20/28 (71)	32/59 (54)	2.1 (0.8-5.5)	0.121
Pietermaritzburg site	15/28 (54)	27/59 (46)	1.4 (0.6-3.4)	0.495
Enrolled in 2014	20/28 (71)	38/59 (64)	1.4 (0.5-3.7)	0.517
Alcohol use ^a	8/20 (40)	5/21 (24)	2.1 (0.6-8.2)	0.269
Smoking ^a	3/20 (15)	5/21 (24)	0.6 (0.1-2.8)	0.474
Underlying medical condition (not HIV) ^d	2/28 (7)	0/59 (0)	11.2 (0.5-242.0) ^c	0.123
Currently taking treatment for tuberculosis	2/23 (9)	1/56 (2)	5.4 (0.5-62.9)	0.178
Received influenza vaccine	0/24 (0)	1/55 (2)	0.7 (0.1-18.9) ^c	0.856
Influenza type A (vs B)	24/28 (86)	53/59 (90)	1.5 (0.4-5.7)	0.579
Influenza type and subtype				
A(H1N1)pdm09				
A(H3N2)	6/28 (21)	11/59 (19)	Reference	Reference
A(unsubtyped)	17/28 (61)	40/59 (68)	0.8 (0.2-2.4)	0.669
B				
	1/28 (4)	2/59 (3)	0.9 (0.1-12.3)	0.948
	4/28 (14)	6/59 (10)	1.2 (0.2-6.1)	0.807
Influenza cycle threshold (Ct) value <30	21/28 (75)	41/58 (71)	1.2 (0.4-3.5)	0.674
Viral coinfection ^b	5/28 (18)	13/59 (22)	0.8 (0.2-2.4)	0.650
Pneumococcal colonisation	6/14 (43)	29/39 (74)	0.25 (0.1-0.9)	0.036
Sore throat	13/24 (54)	22/56 (39)	1.8 (0.7-4.8)	0.221
Runny nose	21/24 (88)	44/56 (79)	1.9 (0.5-7.5)	0.337
Headache	16/24 (67)	25/56 (45)	2.5 (0.9-6.7)	0.075
Myalgia	7/24 (29)	11/56 (20)	1.7 (0.6-5.1)	0.353

Household characteristics				
>3 people per room	8/28 (29)	18/59 (31)	0.9 (0.3-2.5)	0.853
Number in household (excluding index case)				
2-3	14/28 (50)	16/59 (27)	Reference	Reference
4-6	11/28 (39)	38/59 (64)	0.9 (0.3-2.5)	0.644
7+	3/28 (11)	5/59 (8)	0.5 (0.3-0.8)	0.027
Child <5 years in the house (excluding index case)	9/28 (32)	14/59 (24)	1.5 (0.6-4.1)	0.410
≥2 secondary cases in household	2/28 (7)	16/59 (27)	0.2 (0.04-0.9)	0.021
Smoke exposure in home	3/19 (16)	4/38 (11)	1.6 (0.3-7.9)	0.574
Home has a tap inside	4/19 (21)	14/39 (36)	0.5 (0.1-1.7)	0.241
Soap available for hand washing	10/19 (53)	20/38 (53)	0.6 (0.3-3.0)	0.969
Cook with electric stove	18/19 (95)	36/39 (92)	1.5 (0.1-15.4)	0.721

OR – Odds ratio, CI – confidence interval

Data missing for alcohol use (n=4), smoking (n=4), current tuberculosis treatment (n=8), received influenza vaccine (n=9), influenza cycle threshold value (n=1), pneumococcal colonization (n=39), symptoms (sore throat, runny nose, headache and myalgia) (n=7), smoke exposure in home (n=30), tap inside home (n=29), soap available (n=30), cook with electric stove (n=29). Additional factors evaluated but not found to be associated with HIV status of the index case: sharing eating utensils with contacts, avoiding contact with household members, sharing a bed with the index case.

^aIndividuals aged >15 years

^bTest positive on polymerase chain reaction for at least one of parainfluenza virus types 1-3, respiratory syncytial virus, enterovirus, human metapneumovirus, adenovirus or human rhinovirus

^cEstimated using Firth logistic regression

^dAsthma, other chronic lung disease, chronic heart disease, liver disease, renal disease, diabetes mellitus, immunocompromising conditions excluding HIV infection, neurological disease or pregnancy. Comorbidities were considered absent in cases for which the medical records stated that the patient had no underlying medical condition or when there was no direct reference to that condition.

Supplementary table 2: Characteristics of index case and household contacts associated with household secondary infection risk (SIR) individuals testing influenza positive on day 12 visit, Klerksdorp and Pietermaritzburg in South Africa, 2013-2014

Characteristic	SIR ^a n/N (%)	Univariate OR (95% CI)	p	Multivariable OR (95% CI)	p
Index case characteristics					
Age group (years)					
<1	0/6 (0)	Not estimated		Not estimated	
1-4	26/62 (42)	2.5 (1.2-5.4)	0.016	3.3 (1.1-9.7)	0.032
5-14	19/86 (22)	Reference	Reference	Reference	Reference
15-24	13/56 (23)	1.1 (0.4-2.5)	0.884	1.9 (0.7-5.7)	0.232
25-44	21/85 (25)	1.2 (0.5-2.8)	0.742	4.8 (1.1-22.7)	0.048
45-64	4/38 (11)	0.4 (0.1-2.6)	0.343	1.6 (0.2-14.9)	0.684
≥65	0/0 (0)	Not estimated		Not included	
Sex					
Male	32/122 (26)	1.1 (0.6-2.1)	0.736		
Female	51/211 (24)	Reference	Reference		
Site					
Klerksdorp	55/177 (31)	2.1 (1.2-4.0)	0.033		
Edendale	28/156 (18)	Reference	Reference		
Year					
2013	21/108 (19)	Reference	Reference		
2014	62/225 (28)	1.6 (0.8-2.9)	0.143		
HIV status					
Uninfected	64/220 (29)	Reference	Reference	Reference	Reference
Infected	19/113 (17)	0.5 (0.2-1.2)	0.112	0.3 (0.1-0.9)	0.042
HIV status					
Uninfected	64/215 (30)	Reference	Reference		
Infected, receiving ART	14/77 (18)	0.5 (0.2-1.6)	0.257		
Infected, not receiving ART	5/36 (14)	0.4 (0.1-0.8)	0.016		
Non HIV underlying illness ^d					
Absent	83/326 (25)	Not estimated			
Present	0/7 (0)				
Currently taking treatment for tuberculosis					

No					
Yes	66/281 (23)	Reference	Reference		
	9/15 (60)	4.9 (2.2-10.9)	0.002		
Alcohol use ^c					
No	24/89 (27)	2.8 (0.9-8.0)	0.038		
Yes	5/43 (12)	Reference	Reference		
Smoking ^c					
No	25/108 (23)	1.5 (0.5-4.8)	0.476		
Yes	4/24 (17)	Reference	Reference		
Influenza type					
A	71/288 (24)	Reference	Reference		
B	12/39 (31)	1.4 (0.5-4.3)	0.517		
Influenza type and subtype					
A(H3N2)	57/219 (26)	1.6 (0.7-3.3)	0.242		
A(H1N1)pdm09	12/65 (18)	Reference	Reference		
B	12/39 (31)	1.9 (0.6-6.6)	0.275		
A (Unsubtyped)	2/10 (20)	1.1 (0.2-7.9)	0.921		
Influenza cycle threshold (Ct) value					
<30	68/243 (28)	2.1 (1.0-4.1)	0.042	2.4 (1.1-5.2)	0.031
≥30	14/88 (16)	Reference	Reference	Reference	Reference
Pneumococcal colonisation					
Yes	38/131 (29)	0.9 (0.4-2.1)	0.744		
No	24/75 (32)	Reference	Reference		
Viral coinfection ^b					
Yes	18/64 (28)	1.2 (0.6-2.4)	0.553		
No	65/269 (24)	Reference	Reference		
Received influenza vaccine					
Yes	0/5 (0)	Not estimated			
No	74/298 (25)				
Sore throat					
Yes	23/135 (17)	0.5 (0.2-0.9)	0.030		
No	53/173 (31)	Reference	Reference		
Myalgia					
Yes	9/64 (14)	0.4 (0.1-1.2)	0.119		
No	67/244 (27)	Reference	Reference		

Household contact characteristics					
Age group (years)					
<1	3/6 (50)	3.1 (0.8-12.7)	0.113	1.5 (0.4-5.4)	0.503
1-4	14/28 (50)	3.1 (1.2-8.1)	0.023	3.7 (1.3-10.5)	0.016
5-14	20/82 (24)	Reference	Reference	Reference	Reference
15-24	11/76 (14)	0.5 (0.2-1.2)	0.121	0.5 (0.2-1.1)	0.088
25-44	18/84 (21)	0.8 (0.4-1.8)	0.668	0.8 (0.4-1.9)	0.635
45-64	11/40 (28)	1.2 (0.5-3.0)	0.734	1.1 (0.4-3.5)	0.816
≥65	6/17 (35)	1.7 (0.6-5.1)	0.348	2.0 (0.6-7.4)	0.253
Sex					
Male	28/109 (26)	1.0 (0.6-1.8)	0.893		
Female	50/200 (25)	Reference	Reference		
HIV status					
Uninfected	41/140 (29)	Reference	Reference		
Infected	5/26 (19)	0.6 (0.2-1.9)	0.351		
Non HIV underlying illness^d					
Absent	80/321 (25)	Reference	Reference		
Present	3/12 (25)	1.0 (0.3-3.6)	0.995		
Alcohol use^c					
No	33/145 (23)	Reference	Reference		
Yes	11/57 (19)	0.8 (0.4-1.8)	0.614		
Smoking^c					
No	37/169 (22)	Reference	Reference		
Yes	7/33 (21)	1.0 (0.4-2.5)	0.934		
Received influenza vaccine					
Yes	2/12 (17)	Reference	Reference		
No	60/259 (23)	1.5 (0.3-7.5)	0.611		
Share a bed with the index case					
Yes	32/86 (37)	2.2 (1.2-3.9)	0.008	2.7 (1.4-5.3)	0.004
No	48/226 (21)	Reference	Reference	Reference	Reference
Number of people in household					
3-4	15/85 (18)	Reference	Reference	Reference	Reference
4-7	46/195 (24)	1.4 (0.7-3.1)	0.344	1.7 (0.6-4.9)	0.299
>7	22/53 (42)	3.3 (1.1-9.6)	0.027	4.2 (1.1-16.4)	0.035

Number of children aged			
<5 years in house			
≤ 2			
>2	70/315 (22)	Reference	Reference
	13/18 (72)	9.1 (3.1-26.4)	<0.001

OR – Odds ratio, CI – confidence interval. For each characteristic, all available data were included in the analysis. Odds ratios and p values for all variables included in the multivariable models are displayed in the two right hand columns of the table. No pairwise interactions were included in the multivariable models as no interaction terms were found significant. Additional factors evaluated but not found to be associated with SIR: pneumococcal colonisation, viral coinfection, index case myalgia, index case runny nose, crowding (≥ 3 people per room), sharing eating utensils with the index case, avoiding contact with the sick household member.

Missing data: Out of 87 index cases included in the analysis data were missing for alcohol use (n=4), smoking (n=4), current tuberculosis treatment (n=8), received influenza vaccine (n=8), influenza cycle threshold value (n=1), pneumococcal colonization (n=34), symptoms (sore throat, runny nose, headache and myalgia) (n=7). Out of 333 household contacts included in the analysis data were missing for contact sex (n=24), contact HIV status (n=167), contact alcohol use (n=15), contact smoking (n=15), contact influenza vaccine receipt (n=62), contact sharing a bed with index (n=21).

^aSecondary infection risk (SIR)=Number of secondary cases in the household/number of exposed household contacts

^bTest positive on polymerase chain reaction for at least one of parainfluenza virus types 1-3, respiratory syncytial virus, enterovirus, human metapneumovirus, adenovirus or human rhinovirus

^cSelf reported, among individuals aged >15 years

^dAsthma, other chronic lung disease, chronic heart disease, liver disease, renal disease, diabetes mellitus, immunocompromising conditions excluding HIV infection, neurological disease or pregnancy. Comorbidities were considered absent in cases for which the medical records stated that the patient had no underlying medical condition or when there was no direct reference to that condition.

Supplementary table 3: Reported symptoms among household contacts testing influenza positive by age group, Klerksdorp and Pietermaritzburg in South Africa, 2013-2014

Symptom	All ages	<5 years	≥5 years	p
	N=58	N=11	N=47	
	n (%)	n (%)	n (%)	
Fever	29 (50)	7 (64)	22 (47)	0.315
Cough	42 (72)	11 (100)	31 (66)	0.023
Nasal congestion	39 (67)	11 (100)	28 (60)	0.010
Sore throat	27 (47)	5 (45)	22 (47)	0.935
Muscle pains	21 (36)	1 (9)	20 (43)	0.038
Headache	32 (55)	3 (27)	29 (62)	0.039
Diarrhoea	13 (22)	1 (9)	12 (26)	0.239
Any symptom	46 (79)	11 (100)	35 (74)	0.060
≥2 symptoms	41 (71)	10 (91)	31 (66)	0.102
Fever and cough	28 (48)	7 (64)	21 (45)	0.257